REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

The claims have been amended as follows:

1) "A case" in the claims as pointed out by the Examiner has been amended to "a subject".
2) "Administering" in claims 13-16 has been amended to "topically administering". See page 13, lines 11-12 of the specification.
3) "Somatostatin receptor agonist" in claims 13-16 has been limited to "somatostatin receptor SSTR2 or SSTR4 agonist". See page 13, lines 4-5 of the specification.
4) "Corneal sensitivity" in claim 14 has been amended to "decreased corneal sensitivity associated with corneal nerve damage". See page 29, lines 10-11.
5) "Dry eye" in claim 15 has been amended to "dry eye associated with decrease of corneal sensitivity". See page 29, lines 12-13.

A new title has been added which is more descriptive of the claimed invention.

Accordingly, the objection to the title is deemed to be overcome.

A revised Sequence Listing has been added to recite the amino acid sequence of Formula I on page 3 as SEQ ID NO: 3. Formula XI on page 7 of the specification is not subject to the Sequence Listing requirement since it contains a D-amino acid. Please see 37 CFR 1.821(a)(2). No new matter has been added. The sequences set forth in the Sequence Listing are identical to the sequences set forth in the computer readable copy of the Sequence Listing enclosed herewith.

Accordingly, the objection to the specification for lacking an acceptable Sequence Listing is deemed to be overcome.

Claims 13-16 are objected to on the basis of informalities. These informalities have been overcome by the foregoing amendments.

Accordingly, the objection to the claims is deemed to be overcome.

Claims 13-16 are rejected under 35 USC 112, first paragraph, as lacking enablement.

This ground of rejection is respectfully traversed as applied to the amended claims.

The present invention has been made based on the first finding that somatostatin receptors SSTR2 and SSTR4 are present in the trigeminal nerve, where further studies have

established that, as shown in Experimental Examples, the above-mentioned somatostatin receptor agonists have a nerve axon extension action in rabbit trigeminal nerve cells as well as a corneal sensitivity function.

As described in the specification at page 1, lines 17-20, it is reported that lacrimal hypofunction gives rise to corneal hyposensitivity in patients with dry eye, which, upon combination with further lacrimal hypofunction, problematically aggravates the condition of the corneal surface. The present specification teaches that corneal epithelium defect and dry eye can be treated by improving the corneal sensitivity function.

For example, Reference 1 enclosed herewith (CLAO Journal, July 2000, Vol. 26, pp. 159-165) describes that the lacrimal gland and cornea become a tightly integrated unit in the creation of diseases, lacrimal gland disease alters the ocular surface and ocular surface disease alters the lacrimal gland, "corneal lacrimal gland feedback model" (p. 159, abstract, p. 161, right column, lines 39-45, p. 162, left column, Figure 1). Furthermore, Figure 1 shows that decreased corneal sensitivity reduces tear flow and induces corneal damage, which in turn causes lacrimal gland damage, and that they form a vicious circle.

Reference 2 enclosed herewith (Current Opinion Ophthalmol., 2000, Vol. 12, pp. 318-322) describes that the main cause of superficial punctate keratopathy, etc. is decreased corneal sensation, which decreases feedback to the lacrimal gland and reduces tear production (p. 318, abstract, p. 321, right column, lines 18-21). In addition, Reference 3 submitted with the IDS on April 29, 2005 as Reference BL (Cornea. 1996, Vol. 15, pp. 235-239) describes that the decreased tear secretion in dry eye may have an impact on the pathologic changes of the corneal epithelium and may lead to a decline in corneal sensitivity (p. 238, right column, lines 44-47).

Moreover, Reference 4 enclosed herewith (Cornea. July 1996, Vol. 15, No. 4, pp. 368-372) reports that aldose reductase inhibitors can improve corneal epithelial changes caused by diabetes, probably through recovery of corneal sensation and tear production to improve corneal epithelial disorders (specifically, p. 368, abstract, right column, lines 18-20).

From the foregoing, the somatostatin receptor SSTR2 and SSTR4 agonists clarified by the present invention to recover corneal sensation are considered to improve tear dynamics and corneal epithelial disorders. Those skilled in the art will readily understand, given the *in vivo* effect in Experimental Example 3, that a somatostatin receptor agonist shown to provide *in vivo* recovery of corneal sensitivity can be used for the recovery of a corneal epithelial disorder.

Accordingly, it is respectfully submitted that the amended claims are enabled by the specification.

Accordingly, this ground of rejection is deemed to be overcome.

Claims 13-16 are further rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement for the reasons set forth. This ground of rejection is respectfully traversed as applied to the amended claims.

The Examiner holds that the specification should provide characteristics sufficient to specify and distinguish the genus.

To comply with the holding of the Examiner, the somatostatin receptor agonist has been limited to somatostatin receptor SSTR2 or SSTR4 agonist, and the target diseases of the present invention to those recited above. Hence, it is respectfully submitted that the rejection is overcome. Furthermore, new claims 18-22 are added wherein the preferable compounds of the above-mentioned agonists are limited to the four kinds of compounds described in the Examples.

The present specification sufficiently discloses the somatostatin receptor agonists usable for the claimed method (p. 11, line 17 to p. 12, line 24). In addition, the somatostatin receptor agonists usable for the claimed method can also be confirmed using a screening method known to those having ordinary skill in the art.

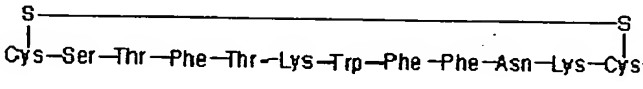
For example, WO 98/44922 disclosing compound 1 of the present application discloses a screening method of somatostatin receptor agonist (WO 98/44922, p. 90, lines 11-32), and the present specification states that the claimed method can employ the somatostatin receptor agonist described in WO 98/44922. Also, WO 97/43278 disclosing compound 2 of the present invention also discloses a screening method of somatostatin receptor agonist (WO 97/43278, p. 32, lines 7-17), and the present specification states that the claimed method can employ the somatostatin receptor agonist described in WO 97/43278. By interpreting the claim while referring to the present specification, those having ordinary skill in the art can understand that the somatostatin receptor agonist usable for the method of the present invention does not include merely any compound, but can identify the agonist with ease.

The Examiner has also admitted, as described in Experimental Example 1, the present invention has been made based on the first finding that somatostatin receptors SSTR2 and SSTR4 are present in the trigeminal nerve, as described above.

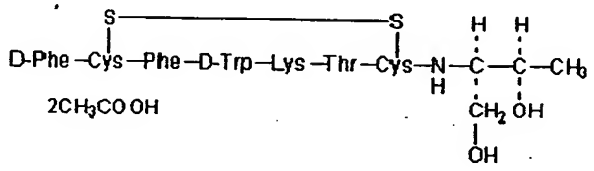
Somatostatin and the somatostatin receptor agonists used in Experimental Examples 2-5 of the present invention are shown in the following drawing (FIGURE). It is known that somatostatin and Octreotide are nonselective somatostatin receptor agonists, Compound 1 is a selective somatostatin receptor SSTR2 agonist, and Compound 2 is a selective somatostatin receptor SSTR4 agonist. Combined with the results obtained in the presence of somatostatin receptors SSTR2 and SSTR4, the presence of the same nerve axon extension promoting action by the compounds having completely different chemical structures means that the effect is irrelevant to the action of individual compounds but afforded by a mechanism via a somatostatin receptor. Accordingly, the present invention teaches that somatostatin receptor SSTR2 or SSTR4 agonist is usable for the claimed method.

Given the *in vivo* effect of Experimental Example 3, those skilled in the art will readily understand that a somatostatin receptor agonist shown to have an *in vitro* corneal nerve axon extension promoting action can be used for the corneal nerve axon extension promoting action *in vivo* and recovery of corneal sensitivity. The diseases recited in claims 14-16 are dry eye and corneal epithelial defect caused by a decline in the corneal sensitivity. Therefore, the relationship between the diseases of claims 14-16 and somatostatin receptor agonist is clear.

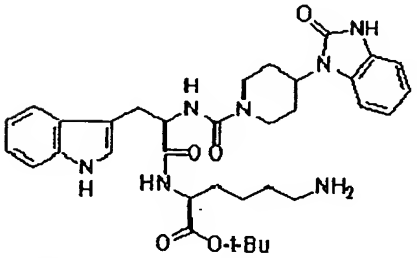
FIGURE



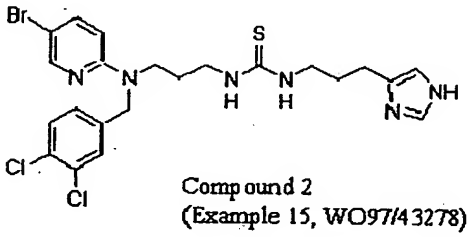
Somatostatin



Octreotide



Compound 1
(Example 4, WO98/44922)



Compound 2
(Example 15, WO97/43278)

Accordingly, this ground of rejection is deemed to be overcome.

Claims 13-16 are rejected under 35 USC 102 as anticipated by Nordisk, WO 98/58646. This ground of rejection is respectfully traversed as applied to the amended claims.

WO 98/58646 describes that certain somatostatin receptor agonists can be used for the treatment of glaucoma, stroma keratitis, iritis, retinitis, cataract and conjunctivitis. However, no pharmacological data supportive of the use of the agonists for the recited diseases or a description comparative thereto is available. In addition, WO 98/58646 does not disclose or suggest (i) a method of promoting extension of corneal nerve axon, (ii) a method of recovering decreased corneal sensitivity associated with corneal nerve damage, (iii) a method of treating dry eye associated with decrease of corneal sensitivity and (iv) a method of treating corneal epithelium defect associated with decrease of corneal sensitivity of claims 13-16 of the present invention.

Although WO 98/58646 describes stroma keratitis as a disease of cornea, stroma and epithelium are different tissues in the cornea. Furthermore, since stroma keratitis, iritis, retinitis and conjunctivitis are inflammatory diseases, the invention of WO 98/58646 is interpreted as aiming at the treatment of inflammatory diseases. In addition, although the Examiner holds, through the reports of Suzuki et al. and Fini et al. that WO 98/58646 discloses inherently possible treatments of corneal epithelium defect of claim 16, the present invention aims at treating the claimed diseases by promoting extension of corneal nerve axon in the cornea with damaged corneal nerve. The present invention does not aim at treating inflammations or corneal epithelium defect associated with inflammations.

WO 98/58646 describes, "the route of administration may be any route which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral, the oral route being preferred." (p. 33, lines 18-20). However, in the treatment method of the present invention, the administration route is "topically to the eye".

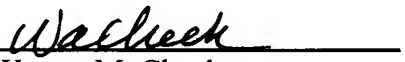
To conclude, the claimed invention has novelty, since it is different from WO 98/58646 in the target disease and the administration route.

Accordingly, this ground of rejection is deemed to be overcome.

In view of the foregoing, it is respectfully submitted that each ground of rejection set forth in the Official Action has been overcome, and that the application is now in condition for allowance. Accordingly, such allowance is solicited.

Respectfully submitted,

Yoshiko TAKAYAMA et al.

By: 

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April 14, 2008

Reference 1

CONRAD BERENS LECTURE

Why the Eye Becomes Dry: A Cornea and Lacrimal Gland Feedback Model

William D. Mathers, MD

Purpose: Many explanations have been offered for why a large segment of the population develops dry eye. The purpose of this paper is to describe a new unifying theory of dry eye that incorporates all of these causes.

Methods: Data from the Department of Ophthalmology, University of Iowa Hospitals and Clinics was analyzed from 520 patients with dry eye, blepharitis and other conditions to assess the relationship between dry eye and blepharitis. This data was reviewed in terms of the relationship between dry eye, menopause, and aging. Also examined in detail were many of the proposed causes for dry eye in the literature.

Results: A close relationship between corneal damage and lacrimal gland function is hypothesized. Not only does decreased lacrimal gland output damage the ocular surface, but also damage to the corneal surface creates a negative feedback loop and damage to the lacrimal gland. There are probably several mechanisms by which this feedback occurs. One mechanism results from interruption or damage to the sensory corneal nerves. Damage to the nerves within the lacrimal gland may be another mechanism. Alteration of growth factor levels in the lacrimal gland, which occurs following corneal damage, represents another possible mechanism. Contact lenses and corneal refractive surgery are additional elements that may create negative feedback to the lacrimal gland.

Conclusion: The ocular surface and the lacrimal gland functions as a tightly integrated unit. Dry eye conditions damage the ocular surface and this in turn leads to further damage to the lacrimal gland.

Introduction

It is universally understood that dry eye is a very frequently encountered problem in ophthalmology. Data from the last few years has made our determination of prevalence of this disease more precise but this determination is hampered by the non-specificity of both the symptoms and the difficulty in applying measurable physiologic tests to determine the diagnosis. Many of these studies are based on patients' subjective reports of symptoms.[1-3] Unfortunately, these symptoms are not specific for dry eye and can easily be confused with blepharitis and seasonal allergies among other entities. Moreover, there is no single measure to determine the presence of dry eye.[4,5] Tear osmolarity appears to be reasonably specific but the range of tear osmolarity in the normal population is quite wide and the test is not widely used. It is, therefore, usually necessary to use a series of tests to evaluate patients for dry eye. These tests often include tear volume and tear flow, vital dye staining of the cornea and conjunctiva, Schirmer's test with or without anesthesia, and impression cytology.

Most studies have estimated that the prevalence of dry eye is 10–20% of the adult population.[1,6-8] Conventional wisdom has long suggested that women represent the bulk of patients suffering from dry eye and this is particularly true for in women in menopause. Our own published studies have shown that 20% of women in menopause complain of dry eye symptoms.[9] More recent studies of the prevalence of symptoms in the adult population indicate the difference in prevalence of dry eye symptoms between men and women is not as great as expected.[3,10] It is also commonly believed that the older population

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TABLE I Dry eye and blepharitis correlations (N = 520 patients)

	P-value
Dry eye (Schirmer's) vs gland dropout (neg)	.02
Dry eye (Schirmer's) vs lipid viscosity (neg)	.01
Tear volume vs lipid viscosity (neg)	.0001
Tear volume vs lipid volume (pos)	.0001
Tear flow vs lipid viscosity (neg)	.0001
Tear flow vs lipid volume (pos)	.0001

56% of patients with blepharitis had dry eye.

48% of patients with obstructive meibomian gland dysfunction had dry eye.

79% of patients with seborrheic meibomian gland dysfunction had dry eye.

has more dry eye symptoms than the younger population. There is little data to confirm this fact, however. Schein found that 14% of the elderly suffer from dry eye symptoms. This is not much different from the general adult population.[10] This finding is somewhat unexpected and counterintuitive since tear function declines with age.[11,12] Some other factors in addition to simple tear production capacity must be affecting the creation of dry eye. Contact lens patients also appear to suffer frequently from dry eye symptoms.[13] Of the 25 million contact lens wearers in the US, approximately 5% stop wearing their lenses during any given year. Most discontinue lens wearing because of difficulties associated with dry eye. Blepharitis patients also complain of dry eye symptoms. It was reported in 1987 that a close relationship exists between dry eye and all forms of blepharitis.[14]

Methods and results

Our data (from the Department of Ophthalmology, University of Iowa Hospitals and Clinics) analyzing a very large database from the normal population and subjects with ocular surface disease indicated a strong correlation between dry eye and many physiologic parameters associated with blepharitis, including lipid viscosity, lipid volume, and gland dropout (Table I). We have also found that a high percentage of both obstructive and seborrheic meibomian gland dysfunction patients have dry eye.

The cause of dry eye however has remained elusive. There has been much research to formulate theories explaining why some of the population suffer from dry eye and the rest do not. Possible explanations that have been offered over the years include immune disease, ocular surface evaporation problems, loss of hormone support for the lacrimal gland or ocular surface, age effects, overstimulation damage to the lacrimal gland, viral disease affecting lacrimal gland function, and blepharitis. Each explanation has received considerable study, and there is data to support all of them.

Immune disease is undoubtedly a significant cause of dry eye.[15] Sjogren's syndrome appears to cause approximately 10% of the cases of dry eye. In our data from over 400 subjects with dry eye from all causes, we found 10% had Sjogren's Syndrome. This is similar to other published results.[8] The disease occurs almost exclusively in women and usually presents as a relatively severe decrease in tear flow combined with ocular surface inflammation.[15] Although autoimmune disease is relatively common in the population, Sjogren's syndrome and its variants cannot account for the majority of dry eye. Denervation may play a role in the loss of tear function in Sjogren's syndrome, as changes in lacrimal gland enervation appear to precede lacrimal gland destruction.[16]

Evaporation also plays a role as a causative agent in dry eye, although the average evaporation rate from the ocular surface is only a small amount of water.[17] Approximately one third of the resting tear flow evaporates in the normal eye. This increases to 75% of the total tear flow in the dry eye. Evaporation still represents a relatively small percentage of the potential maximum tear flow (Table II). We found the total steady state flow in the dry eye and the normal was approximately equal. Therefore, increased evaporation cannot be the sole cause of dry eye, although it undoubtedly contributes to the disease process.

Altered hormonal support of the lacrimal gland also causes dry eye.[18] Considerable animal and human data has been collected over the years to support the concept that androgens are important in driving lacrimal function. Androgen receptors have been found in the lacrimal gland while estrogen receptors have not.[19] However, serum testosterone levels do not correlate well with tear function.[9] It is most likely that serum testosterone levels do not reflect the more relevant androgenic environment in the lacrimal gland.

Data suggest that androgens are generated within the lacrimal gland and would not be reflected in the serum levels. Part of the key androgen action in the lacrimal gland may be related to its immune modulation. Androgens generally suppress immune response and this could easily effect the immune status of the lacrimal gland.[20-22] Prolactins also appear to play a role in lacrimal gland function. Our research has shown a negative correlation between serum prolactin levels and lacrimal function in humans.[9] There is evidence that the lacrimal gland produces its own prolactin.[23] Prolactins are immunomodulating and their action may counteract androgen functions.

TABLE II Tear evaporation in normal and dry eye patients

Evaporation in normals*	
Tear flow normal	0.2–0.4 µL/min
Evaporation	11–15x10^{-7}gms/cm^2/sec = 0.1-0.15 µL/min
Total Flow	0.3 +0.15 = 0.45 µL/min
Evaporation in dry eye patients†	
Tear flow dry eye	0.1–0.15 µL/min
Evaporation	30–40x10^{-7}gms/cm^2/sec = 0.3–0.4 µL/min
Total dry eye flow	0.45 µL/min

**33% of the total tear flow in the normal evaporates.*

†75% of the total tear flow in the dry eye evaporates.

Prolactin can have a direct effect on the functional status of the lacrimal gland.[24] Estrogen does not appear to play a role in lacrimal gland function despite the strong evidence that menopause has long been associated with the development of dry eye. Nor does estrogen therapy appear to alter the development of dry eye in women. (Mathers, unpublished)

Mircheff and coworkers have proposed an interesting hypothesis regarding overstimulation of the lacrimal gland.[25] Any stress that induces increased tear production would necessitate an increase in stimulus to the lacrimal gland. Such increased stimulus, they hypothesize, creates abnormalities in the cellular trafficking of lacrimal acini organelles. This alters the antigenicity of the acinar cells and leads to immune disease. While there is no direct evidence that this is a factor in the development of dry eye, their experimental data is very promising.

Virtually all tissues of the body demonstrate some effects of aging and the lacrimal gland is no exception. Although there is little data indicating what cellular changes occur with aging, tear function declines slowly with age. There is some epidemiological evidence to support this concept.[26–29] While Schein has shown that only 15% of the elderly population suffer from dry eye, which is not a higher incidence than that found in younger subjects, Craig demonstrated a decline in tear function in women with age.[30] Our own research has identified a marked decline with age in women for virtually all of our tear perimeters, including tear volume, tear flow, evaporation, and reserve capacity (Schirmer's test without anesthetic).[11] Nevertheless, the majority of older people do not have dry eye symptoms. The cause of this age effect remains undetermined but declining hormonal support and damage to the lacrimal gland from inflammation are likely causes. The rat model has shown a decrease in size in a number of secretory vesicles and an increase of inflammatory cells with age.[31] There is also an increased expression of MHC Class II molecules in human lacrimal cells with aging.[32]

Another intriguing hypothesis for the cause of dry eye is viral disease. Viruses such as Epstein Barr can infect the lacrimal gland and diminish its capacity or alter its antigenicity leading to chronic disease and decreased function output. Epstein Barr virus has been detected in the tears of dry eye patients by Tsubota.[33] It is likely that this type of viral process is the cause of dry eye in at least some young people. It is unlikely, however, that this represents a major or even a highly significant cause of dry eye.

The close association between blepharitis and dry eye has been recognized for a long time. Both cause similar symptoms and it has often been reported that patients with one disease frequently suffer from the other.[14,34] Blepharitis often causes increased evaporation that could directly lead to dry eye in those patients with already diminished capacity.[35] Evaporation would also stress the system and could activate other mechanisms noted above. Seborrheic meibomian gland dysfunction, however, is usually associated with decreased evaporation. These patients, nevertheless, very frequently have dry eye. Since few careful epidemiological studies have been performed, it is possible that blepharitis patients with dry eye simply need medical attention more frequently than those without dry eye, altering our appreciation of the incidence of dry eye within the blepharitis group. It is also likely that dry eye partially creates or exacerbates blepharitis by decreasing the flushing action of tears on the lid margin and decreasing the washout of inflammatory mediators from the tear film, leaving them to act on the lid margin. An analysis of our database (approximately 520 patients) with a mixture of dry eye, blepharitis, and normal subjects indicated a very strong correlation between dry eye tear function and all blepharitis parameters. We found the incidence of dry eye was three times more common in the blepharitis population than the 15–20% incidence found in the normal population. This strong correlation between blepharitis and dry eye indicates a relationship between these two entities which remains poorly understood (Table I).

Lacrimal secretions contain a complex mix of many factors. An important element in tears are various growth factors necessary for corneal and conjunctiva epithelial health.[36–38] A decline in these growth factors would logically lead to dysfunction of the epithelial surface and create or worsen dry eye symptoms. Pflugfelder and his associate Stern have proposed this process as a logical and probably significant mechanism.[36] Lactoferin and other mediators are important in the protection of the ocular surface from bacteria and this may be important in the genesis of blepharitis and other surface inflammatory syndromes as well. Artificial tears do not replace these factors. This is undoubtedly a major reason for the relative ineffectiveness of artificial tears in restoring the ocular surface to its normal condition.

Discussion

It is very likely that all of these explanations are, at least in part, correct, and most of them are not mutually exclusive. None of them, however, generates a broad enough view of the dry eye to unify all of these observations. What is needed is a new model that incorporates these multiple disease processes and factors. This new model should explain all of the relevant data and should suggest lines of investigation and experiments with predicted results which researchers can pursue. We are proposing a corneal lacrimal gland feedback model as such an explanation. The essence of this model is the relationship between the lacrimal gland and the cornea. The lacrimal gland and cornea become a tightly integrated unit in the creation of disease. Lacrimal gland disease alters the ocular surface and ocular surface disease alters the lacrimal gland (Figure 1).

Normal homeostasis depends upon regulated corneal tear flow as suggested by Dartt.[39] The most likely primary drive for this regulation is tear osmolarity (Figure 2). Increased tear osmolarity causes increased stimulation from the ocular surface and activation of the neural drive that increases tear flow resulting in decreased tear osmolarity. There is strong evidence to suggest that stimulation drives essentially all tear flow.[40] Sleep causes profound decreased in tear flow and general anesthesia also produces a similar decrease.[41,42] Topical anesthesia has also been reported to cause very low tear flow.[40] The concept of a

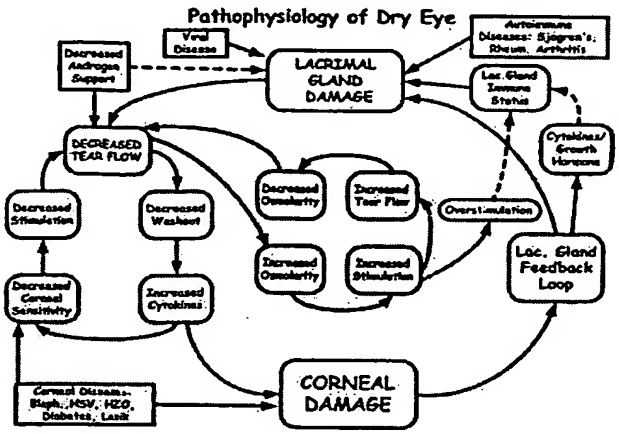

Figure 1 *Pathophysiology of dry eye*

basal secretion versus a reflex secretion, although deeply imbedded in the literature, has little experimental support. Available data indicates essentially all tear flow is stimulated tear flow and there is no difference between reflex (stimulated) tear flow and basal tear secretions.[40] In our investigations of tear flow we have endeavored to measure tear flow by dilution of fluorescein under circumstances that would produce an absolute minimum of ocular stimulation either by bright light, conjunctival or corneal contact, or psychological stimulation from anxiety. We believe this is the main factor that has caused our investigations to find much lower tear flows than other laboratories.[11,17,34]

Figure 3 diagrams multiple factors that can cause decreased tear flow. Any lacrimal gland damage, whether from immune causes, overstimulation, decreased hormonal support, or viral disease would ultimately result in decreased in tear flow with significant consequences. The model predicts that decreased flow would lead to decreased washout and removal of surface debris and bacteria. It would also lead to increased

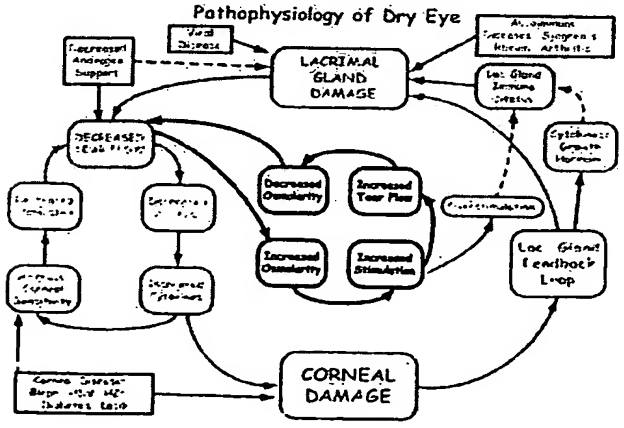

Figure 2 *Pathophysiology of dry eye: tear osmolarity*

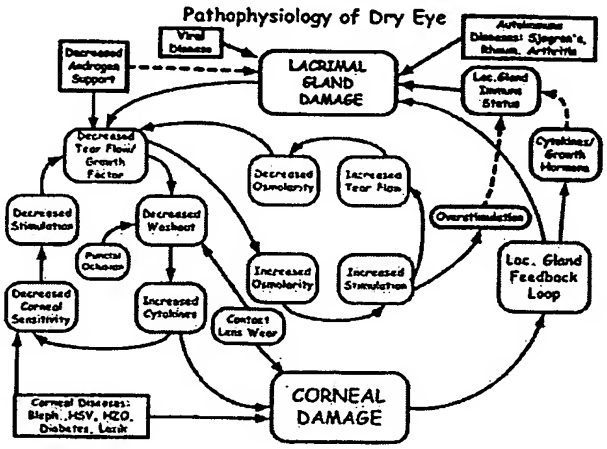

Figure 3 *Pathophysiology of dry eye: multiple factors that can cause decreased tear flow*

residence time for cytokines generated by ocular surface inflammation. Decreased tear flow would also result in decreased growth factors in the tear film available to maintain ocular surface integrity.

If normal stimulation from the ocular surface were compromised, dry eye should result. There are many possible mechanisms that could cause corneal nerve damage and interrupt normal stimulation. Increased cytokine levels in the tear film may cause corneal nerve damage decreasing corneal sensation and lowering tear production. Cytokines appear to inhibit parasympathetic neural transmission in peripheral nerves.[43] Decreased corneal sensitivity has been noted in Sjogren's syndrome, with increased cytokines in the tear film.[44] Rosacea blepharitis patients also have increased cytokine levels in the tear film.[45] Dry eye patients have decreased corneal sensation.[46] Barton found an inverse correlation between IL-1α and tear production.[45] Other diseases are associated with damaged corneal sensation, such as herpes simplex, herpes zoster, and diabetes.[47,48] Wearing of contact lens has long been associated with decreased corneal sensation.[13,49,50] LASIK procedures and other procedures in refractive surgery are known to damage corneal enervation as well.[51-53]

We hypothesize that corneal damage causes significant changes that result in damage to the lacrimal gland (Figure 4). The potential sources of damage to the cornea is large. Contact lenses and punctal occlusion could cause damage from increased residence times of inflammatory cytokines. Many corneal diseases damage the cornea. The evidence for a feedback loop following corneal damage is widespread but incomplete. The higher than expected incidence of dry eye in blepharitis, particularly seborrheic meibomian gland dysfunction, strongly suggest that such a mechanism must exist. Evidence from molecular and cell biology studies are beginning to illuminate some details of this process. There are many potential mechanisms by which this could occur. The most direct evidence we have for this feedback process is from epithelial wounding

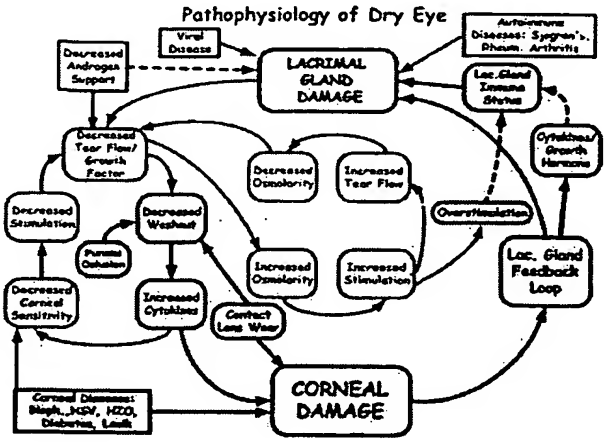

Figure 4 *Pathophysiology of dry eye: corneal damage causes significant changes that result in damage to the lacrimal gland*

studies. Wilson found that messenger RNA levels in the lacrimal gland for hepatocyte growth factor and epidermal growth factor (EGF) were increased following corneal epithelial scrape injuries.[54] EGF expression in the lacrimal gland increases in response to wounding.[55] Cholinergic stimulation of the lacrimal gland increases EGF secretion.[55,56] Corneal wounding increases TNF-α in the lacrimal gland.[57] Corneal injury also stimulates production of fibroblast growth factor (FGF-2) in the lacrimal gland. FGF-2 is known to stimulate prolactin production[58] and prolactin is known to be immuno-modulating.[59,60] Prolactin can have a direct effect on the functional status of the lacrimal gland.[24] Any change in the lacrimal gland that results from corneal damage is evidence that such a feedback mechanism from cornea to lacrimal gland is possible. Wilson has proposed a regulatory arc from cornea to lacrimal gland through parasympathetic innervation.[54]

Other parts of this cornea-to-lacrimal gland feedback mechanism have been previously suggested. Stern hypothesized that changes in lacrimal gland nerves may initiate lacrimal gland damage.[37,38] Meneray, in rabbit studies, found a massive accumulation of secretory granules in the acini following denervation.[61] Stern suggested altered lacrimal innervation may release substance P, stimulating lymphocytes in the lacrimal gland.[37] Decreased corneal sensation to the lacrimal gland may cause atrophy of the lacrimal gland.[38] Nguyen has found that sensory denervation in the lacrimal gland leads to deregulation of protein synthesis.[62] Protein synthesis was actually increased immediately following denervation in this experiment, demonstrating that the relationship between innervation and secretion is probably complex. If decreased stimulation can lead to lacrimal damage, some patients may suffer from the opposite process, overstimulation. As noted above, overstimulation has been suggested as a mechanism that could create abnormal organelle trafficking and damage the lacrimal gland.[25] Additional factors other than this corneal feedback loop may also contribute to lacrimal gland damage. As noted above, decreased androgen support may directly damage the lacrimal gland, lead to atrophy, or alter its immune status. Primary or secondary systematic immune diseases also damage lacrimal gland function.[18] In addition to all of this, decreased corneal sensation appears to be the result of the aging process.[63]

There are a number of critical implications we can derive from this feedback model. Contact lenses present a major perturbation to the ocular surface. Contact lenses most likely decrease washout of the ocular surface by retarding tear flow under the lens. They are also known to decrease corneal sensation, as noted above.[13,49,50] This decreased corneal stimulation would lead directly to decreased tear flow creating a negative feedback. Surface trauma, hypoxia, and inflammation from contact lens wearing could cause corneal damage directly and lead to secondary lacrimal gland damage. Increased cytokines have been found in the tear film of contact lens patients (Figure 4).[64,65]

An appreciation of these complex physiological processes is essential in devising appropriate remedies. Maximizing contact lens function is absolutely critical. The relationship between corneal nerves, tear flow during contact lens wear, and tear cytokines levels needs further study. We believe that the relationship between the contact lens wear, corneal disease, and the eventual development of lacrimal gland disease is the primary explanation why so many people stop wearing contact lenses. Inflamed eyes eventually become dry and this causes further deterioration of tear function. If these physiologic processes were better understood they could be corrected.

Refractive surgical procedures are not a panacea for this process. LASIK procedures may also lead to lacrimal gland damage through the same mechanisms of corneal damage and sensory denervation. Many studies have demonstrated that surgical denervation of the cornea in LASIK patients remains for many months, if not longer.[51,52] Symptoms of dry eye are common after LASIK and are frequently worse than their preoperative condition.[66] Some LASIK patients may require special care to avoid severe dry eye problems.

The role of blepharitis remains central to the creation of dry eye; the two problems are very closely related. This relationship has both positive and negative implications. Interrupting the negative feedback loop by successfully treating the blepharitis is likely to improve lacrimal function. Failure to improve lacrimal function will most likely result in worsening of the blepharitis.

Punctal occlusion has been a popular therapy for dry eye for many years. Nevertheless, it may alter corneal feedback in unexpected ways. Punctal occlusion causes a decrease in outflow, stasis of the tear film, and decreased washout. We expect that cytokine levels might rise following punctal occlusion in some individuals whereas others who appear to benefit clinically may simply have improved tear volumes. Our studies found that while tear flow is not altered following punctal occlusion, tear volume increases. We found no change in osmolarity.[67] For those patients likely to develop increased cytokines, too much punctal occlusion may not be of benefit and may actually increase corneal damage and worsen the dry eye. If the increased tear volume helped restore the epithelial cells to health, however,

punctal occlusion might reverse the negative feedback to the lacrimal gland and improve tear production (Figure 4).

Evaporation continues to represent a central process in the development of blepharitis and dry eye. Controlling evaporation would be very helpful to maintain normal tear osmolarity and minimizing perturbations of the tear film. With normalized osmolarity, healthy epithelial cells are less likely to release inflammatory cytokines. While no method has yet been demonstrated that successfully improves evaporation, research in this field continues.

We have recently studied a new preparation of oral pilocarpine, Salagen, which has been formulated for slow release following oral ingestion. Although originally created to improve saliva production in Sjogren's syndrome patients, our studies indicate it is probably even more effective in stimulating tear flow. All the dry eye patients we have studied showed an increased tear volume and tear flow following a month of Salagen therapy.[68] Improved tear flow and restoration of the washout mechanism should interrupt the damaging feedback process we described above. It may even increase the level of growth hormones in the tear film and thus improve ocular surface health. Naturally produced lacrimal flow is vastly preferable to artificial tears for many reasons. If further work demonstrates that Salagen remains effective in these patients, this represents the first documented evidence of an effective tear stimulant. This could provide a beneficial therapy for millions of dry eye patients.

Conclusions

We have presented a global theory to explain the disease process that results in dry eye. The theory hypothesizes that the lacrimal gland and the ocular surface are a functional unit and that damage to the ocular surface results in lacrimal gland disease. Dry eye is, in part, the end result of a destructive feedback process whereby the corneal damage from compromised tear production leads to further lacrimal gland damage. More research is needed to explore the ramifications of this theory. Effective research will require both clinical information and cell biology investigations that compliment each other. These interactions may be very complex but we believe they are capable of being understood with carefully directed research. Eventually we should be able to create therapies for individual patients, depending on their particular needs, which effectively counteract deleterious feedback mechanisms and restore the ocular surface to a state of health.

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Reference 2

Dry eye after refractive surgery

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Photorefractive keratectomy and laser *in situ* keratomileusis can induce or exacerbate dry eye after surgery. This manifests as an increase in degree and frequency of symptoms, corneal findings, such as superficial punctate keratopathy, and abnormal results of dry eye tests, such as the Schirmer test and tear break-up time. The cause mainly involves decreased corneal sensation, resulting in decreased feedback to the lacrimal gland and reduced tear production. Other causes may include increased evaporation, inflammation, or toxicity of medications. Dry eye may result infrequently in impaired wound healing and decreased optical quality of the cornea, but it is transient, lasting from a few weeks up to 1 year. Patients should be warned about this distressing complication. During a period of dry eye, artificial tears and punctal plugs are helpful in preventing or alleviating patient discomfort. Curr Opin Ophthalmol 2001, 12:318–322

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Abbreviations

EGF	epidermal growth factor
LASIK	laser *in situ* keratomileusis
PARK	photoastigmatic refractive keratectomy
PRK	photorefractive keratectomy
I/STV	Schirmer test without anesthesia/Schirmer test value
II/BTS	Schirmer test with anesthesia/basal tear secretion
TBUT	tear break up time

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Dry eye is an undesirable sequela of refractive surgery. Patients who have undergone photorefractive keratectomy (PRK) and laser *in situ* keratomileusis (LASIK) often report symptoms of dryness, grittiness, or irritation similar to those symptoms experienced by patients with dry eye. Additionally, results of measures of dry eye, such as the Schirmer test, tear break up time, and rose Bengal staining have been reported to be abnormal for a few months postoperatively. With the increasing number of refractive surgeries performed, are we creating a new population of patients with dry eye? In this review, the course of tear-related changes, etiology, sequelae, and management of dry eye after PRK and LASIK will be discussed.

Dry eye is defined as a disorder of the tear film caused by tear deficiency or excessive tear evaporation, which, in turn, causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort [1,2]. Tear-related causes can be attributed to abnormalities in tear production by the lacrimal gland, distribution by blinking, or evaporation from the ocular surface [3]. Diagnosis is made after analyzing subjective complaints, objective signs, and abnormal results of dry eye tests. Because a normal ocular surface with good optical quality is a prerequisite for refractive surgery, pathologic signs are usually not present. Therefore, patient symptoms serve as indicators of the presence of dry eye. These symptoms should prompt a clinician to initiate a series of tests to determine the cause of dry eye, measure the degree of dry eye, and determine the need for preoperative therapy. This information is useful in deciding whether the patient is a good candidate for surgery.

Course of tear-related changes

Refractive surgery is believed to cause tear-deficient dry eye by a neural-based mechanism. Because the standard measure for showing reduced tear volume and tear flow is the Schirmer test, studies consistently have included this test in reporting dry eye incidences. Yu *et al.* [4••] performed a prospective, nonrandomized study that compared the effect of LASIK on symptoms and tear function preoperatively and postoperatively. Before surgery, the authors found that 15.6% of patients experienced dry eye symptoms, 50% had Schirmer I/STV (Schirmer test without anesthesia/Schirmer test value) values less than 10 mm and Schirmer II/BTS (Schirmer test with anesthesia/basal tear secretion) values less than 5 mm, and 63% had a tear break-up time (TBUT) of less than 5 seconds. The high incidence of abnormal test

values was attributed to the large proportion of LASIK patients who had a history of contact lens intolerance. Postoperatively, the incidence of symptomatic subjects was 94.8% at 1 day, 85.4% at 1 week, and 59.4% at 1 month. One month after LASIK, 60% had abnormal Schirmer values and 69% had an abnormal TBUT. Mean Schirmer I and II values decreased by as much as 30%. Subgroup analysis showed that 72% of patients with Schirmer I values less than 10 mm preoperatively experienced dry eyes 1 month after surgery, versus 46% with Schirmer I values > 10 mm. The authors concluded that preoperative Schirmer I values less than 10 mm preoperatively are a significant risk factors for experiencing dry eye symptoms 1 month after LASIK.

Benitez del-Castillo *et al.* [5••] prospectively compared tear secretion and corneal sensitivity on long-term contact lens wearers (more than 5 years) versus non–contact lens wearers after LASIK. In this study, tear secretion and corneal sensitivity were significantly lower in long-term contact lens wearers than in non–contact lens wearers preoperatively and 6 months after surgery. Overall, tear secretion and corneal sensitivity decreased significantly after LASIK and returned to preoperative levels only after 9 months. Aras *et al.* [6•] similarly reported reduced tear secretion 4 weeks after LASIK. Schirmer I values were substantially lower in operated versus control eyes of the same patient who did not undergo surgery.

Changes in tear dynamics also occur after PRK. A study by Ozdamar *et al.* [7] showed a significant decrease in Schirmer I values and TBUT scores 6 weeks after PRK in patients with contralateral eyes who underwent operation compared with patients who did not. Schirmer I and TBUT values were approximately 50% lower than control values. After PRK and photoastigmatic refractive keratectomy (PARK), Siganos *et al.* [8•] found a significant reduction in Schirmer I, Schirmer II, and TBUT values at 1, 3, and 6 months after surgery. The lowest values were observed at 1 month. The values steadily increased, but the values did not reach preoperative levels even at 6 months. The pattern of change on Schirmer I and TBUT of PRK and PARK was similar at all intervals. However, at 3 and 6 months, Schirmer II values after PARK were significantly lower than values after PRK. Possible explanations presented include a dellen effect caused by a more irregular corneal surface or the irregular ablation of corneal nerves affecting reflex secretion after astigmatic treatment.

In a study of tear function changes after PRK and LASIK, Lee *et al.* [9••] showed a significant reduction in Schirmer II and TBUT scores and a significant increase in tear osmolarity 3 months after both procedures. However, there was a greater decrease in Schirmer II and TBUT values and a higher tear osmolarity in LASIK patients than in PRK patients. The authors concluded that the decrease in tear production and severity of dry eye was greater in LASIK than PRK.

Etiology

The ocular surface (cornea, conjunctiva, accessory lacrimal glands, and meibomian glands), the main lacrimal gland, and the interconnecting neural reflex loops comprise a functional unit in which parts act together, forming an "ocular surface lacrimal gland feedback" system [10,11,12••]. When afferent nerves of the ocular surface are stimulated, a reflex results in immediate blinking and secretion of a copious amount of reflex tears from several tissues and glands of the ocular surface that are overwhelmed by the main lacrimal gland. Reflex tearing is important because it supplies such essential components as epidermal growth factor (EGF) and vitamin A, a deficiency which may cause squamous metaplasia [3]. Continuous subthreshold stimulation of the cornea by the lids or environmental factors such as wind is believed to result in a constant low-level secretion from the same sources. In cases of neurotrophic keratitis, in which decreased corneal sensation is the hallmark, there is a reduction in aqueous production [13]. Tear flow and volume were also found to decrease significantly below physiologic values after topical anesthetic instillation. The magnitude of decrease was approximately 60% compared with baseline values without anesthesia in both the younger and the older age groups [14]. Conversely, with a return of corneal sensation, tear flow is expected to improve. Fujishima *et al.* [15] administered oral aldose inhibitors to patients with diabetes and observed an improvement in their corneal sensation. This was accompanied by parallel improvements in Schirmer test values, tear break-up time, and fluorescein and rose Bengal staining. The development of dry eye is consistent with our understanding that refractive surgery disrupts this integrated functional unit by destroying sensory innervation of the central cornea.

Corneal sensation and nerve morphology

Understanding corneal sensation and corneal nerve morphology is important because they are closely related to the course of tear function test changes. Central corneal sensation is mediated by stromal nerves that originate from the long ciliary nerves and penetrate the Bowman membrane. The long ciliary nerve comes from the ophthalmic nerve, which is the first division of the trigeminal nerve [16,17]. In LASIK, the microkeratome makes a tangential cut across the corneal surface. The penetrating nerves are severed, except in the area of the flap hinge. In PRK, the corneal epithelium, along with its nerve endings, are removed by using alcohol, mechanical scrape, a rotating brush, or a laser. The exposed stromal bed is then ablated using the laser, causing further obliteration of the nerves that supply the central

corneal surface. The net result is a loss or decrease in corneal sensation.

After LASIK, corneal sensation was reduced for approximately 3 weeks, with the lowest values observed during the first 2 weeks [18•,19••]. Corneal sensation began to return at 3 weeks, approaching sensitivity values comparable with preoperative levels 6 to 9 months postoperatively [6,17–19]. A different temporal pattern of loss and recovery of corneal nerve function was observed following PRK. Corneal sensitivity was depressed significantly at week 1, with a further reduction at week 2, and gradual recovery reaching preoperative levels at 1 year [20]. Other reports showed that the return to full sensitivity after PRK was achieved between 3 and 9 months [21–23]. The immediate loss at week 1 was caused by the total removal of the corneal epithelial nerve supply and the underlying stromal nerves. The further decrease at week 2 probably was a result of the new epithelium acting as a barrier to stimulation, whereas the gradual recovery afterward was probably caused by epithelial reinnervation within the ablation zone [20].

Comparative studies have been conducted on corneal sensitivity changes after LASIK and PRK. In the correction of low myopia, corneal sensitivity in the ablated zone was depressed further after LASIK than it was after PRK during the first 3 months after surgery. After 6 months, corneal sensitivity values were similar in both groups [24]. For high myopic corrections, patients who underwent LASIK had better corneal sensation after 6 to 12 months than patients who underwent PRK [21]. A possible explanation for this sensory differential is the substantial amount of tissue removed in high myopia, and the additional removal of the epithelium and the Bowman membrane in PRK resulted in a greater nerve tissue loss compared than it did with LASIK. This may require a longer regeneration and recovery time. The preservation of subepithelial nerves in the LASIK flap also may play a role in the differences in corneal sensation.

In human *in vivo* confocal microscopy studies, PRK and LASIK show a similar centripetally oriented regeneration of corneal nerves [25]. Six months after LASIK, the appearance of short, sub-basal nerve fiber bundles in the central area coincided with recovery of sensitivity values comparable with values observed in control subjects [19]. However, further changes in nerve structure were detectable up to 12 months after surgery. Three months after PRK, single nonbranched nerve fibers could be visualized at the center. At 6 to 8 months, subepithelial nerve regeneration seemed to be complete [25]. This is consistent with the recovery of corneal sensitivity observed within 6 to 12 months after PRK.

Other causes

In addition to tear deficiency from a neural mechanism, other causes may contribute to dry eye after refractive surgery. Reduced corneal sensation not only decreases tear secretion but also reduces blink rate [26]. Collins [27] reported that topical proparacaine applied bilaterally decreased the blink rate by approximately 30%. Less blinking and decreased wearing of eyeglasses after refractive surgery can increase the evaporation rate of tears [3,28]. Trauma of the microkeratome pass, suction ring application in LASIK, and epithelial removal after PRK will incite postoperative inflammation. Inflammatory mediators may cause the discomfort and irritation perceived as dry eye symptoms or may aggravate the decreased secretion of the lacrimal gland. Topical medications applied after refractive surgery may have toxic effects on the corneal epithelium. A change in corneal curvature could alter tear dynamics and cause a dellen effect, as observed in astigmatic treatments. It is possible that all these explanations are partly correct, and each may contribute to the symptoms experienced postoperatively. However, most of the evidence points to a predominantly tear-deficient state induced by decreased sensation and reduced reflex tearing.

Sequelae

The prognosis for dry eye after refractive surgery is good. Symptoms develop in most patients that resolve after a limited period of time without permanent complication. Individuals with pre-existing dry eye may experience exacerbation of symptoms, but normal recovery is expected. In patients with non-Sjogren dry eye and contact lens intolerance in whom PRK was thought to be contraindicated, it was shown that re-epithelialization was completed after 4 days, and patients were able to eliminate contact lenses [29]. Additionally, subclinical tear deficiency indicated by low Schirmer test values before surgery reportedly did not influence the visual outcome and haze scores in PRK patients 1 year after surgery [30]. However, dry eye deserves close attention and monitoring because it can have devastating consequences. The tear film bathes, protects, and nourishes the cornea and contains proteins that may be antibacterial. These properties are compromised in dry eye and there is an increased likelihood of impaired wound healing. Superficial punctate keratitis, recurrent epithelial erosion, corneal surface irregularities, flap wrinkles, epithelial ingrowth, and infection are complications that can occur. In addition to the accompanying discomfort, the optical quality of the cornea may deteriorate, rendering the surgery a failure and defeating the purpose of undergoing refractive surgery.

Management

Management of dry eye after refractive surgery begins with a thorough preoperative screening. A comprehensive history and a questionnaire may detect pre-existing disease and determine the need for supplementary tear function tests. The following symptoms are particularly important. The most frequently reported symptoms of

ocular irritation for dry eye were dryness, soreness, and light sensitivity [31,32]. A large number of refractive patients are contact lens wearers, and it is necessary to determine whether they are at an increased risk of development of or aggravation of dry eye after surgery. A history of contact lens wear and a reduction in wearing time has been associated with tear film instability, damage to the ocular surface epithelium, and dry eye symptoms [33–35]. Additionally, tear secretion and corneal sensitivity were found to be more depressed in long-term contact lens wearers preoperatively and 6 months after surgery [4]. Concurrent allergies, dry mouth, or the use of medications can increase the chance of patients reporting dry eye symptoms [36]. In the presence of these warning signs, the surgeon can initiate preventive measures, including rescheduling of surgery, treatment of dry eye preoperatively until symptoms subside, and initiation of therapy immediately after surgery to prevent the recurrence or worsening of symptoms.

Refractive surgery causes a tear-deficient dry eye that is transient, lasting for approximately 6 months to 1 year. Patients should be warned of the discomfort and the possible need for additional eye drops during this period. Symptom-based management is practical and acceptable considering that refractive surgery is an elective procedure, and we prefer not to subject the patient to a battery of uncomfortable, time-consuming tests when symptoms are not present. Therapy should be directed to the specific mechanism, should be convenient for the patient to administer, and should avoid morphologic changes and side effects to the ocular surface that may affect optical quality.

Artificial tears are useful for managing these symptoms. Although we do not routinely dispense artificial tears postoperatively, we do not hesitate to give patients this alternative if they report discomfort consistent with dry eye. One study found that using carmellose-based artificial tears significantly reduced postoperative symptoms of ocular irritation and improved tear film stability 1 month after LASIK [37]. Symptom reduction was accompanied by improvements in tear break-up time, rose Bengal staining, and goblet cell density compared with balanced salt solution treatment.

For patients in whom a higher probability of development of dry eye postoperatively was reasonably suspected, we may insert a collagen punctal plug immediately after the procedure. Punctal occlusion is a simple, popular procedure for managing dry eye. The rationale behind punctal occlusion is to retain natural and artificial tears by blocking tear outflow [38,39]. Collagen-absorbable implants reduce flow through the canaliculus by approximately 60 to 80% and can last from 3 days to 2 weeks [40]. We insert one punctal plug preferably in the inferior punctum to ensure adequate moisture by lowering drainage function. The increased tear volume maintains tear osmolarity and helps to restore the epithelial cells to health. Although it may benefit patients with low Schirmer values, it may cause stasis of the tear film and decrease washout. Fortunately, inflammation and release of possibly harmful cytokines are resolved fairly early after refractive surgery, thereby lessening the chance of increasing corneal damage and worsening dry eye symptoms.

Alternative treatments for dry eye, including sodium hylauronate eyedrops, autologous serum application, and cyclosporin A ophthalmic emulsion, have been reported to be beneficial, but their use in postrefractive surgery dry eye has yet to be investigated [41–43].

Conclusion

Excimer laser refractive surgery induces tear-deficient dry eye and exacerbates pre-existing disease by disrupting corneal innervation. Decreased corneal sensation, dry eye symptoms, abnormal results of the Schirmer test, and tear break-up time values can be present from 6 months to 1 year after surgery. Candidates for surgery should be screened properly so that pre-existing dry eye is detected, and patients should be counseled and pretreated accordingly. Administration of artificial tears and insertion of punctal plugs are recommended as measures to reduce discomfort during the symptomatic postoperative period.

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Decrease in Corneal Sensitivity and Change in Tear Function in Dry Eye

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Our purpose was to investigate the relationship between insufficient tear secretion and decreased corneal sensitivity. We studied 59 patients with dry eye, 15 of whom had Sjögren's syndrome (SS), and 26 healthy subjects. Corneal sensitivity was measured by the esthesiometer of Cochet and Bonnet. Schirmer test with or without anesthesia, tear clearance rate, tear function index, and rose bengal and fluorescein staining were also evaluated. The mean corneal sensitivity of either dry-eye group (4.6±1.2 and 4.5±1.2 cm for non-SS and SS dry eye, respectively) was significantly lower than that of the control (5.8±0.4 cm, $p < 0.001$). Corneal sensitivity correlated significantly with the Schirmer values with anesthesia and the tear function index in the two dry-eye groups and the control ($p < 0.05$). There were significant relationships between corneal sensitivity and the rose bengal and fluorescein scores in the three groups ($p < 0.05$). Hyposecretion of tears in dry eye may lead to pathologic changes in corneal epithelium and a decline in corneal sensitivity. Prompt treatment of dry eye is essential to maintain a normal corneal protective mechanism.

Key Words: Corneal sensitivity—Tear function parameter—Dry eye.

The attenuation of corneal sensitivity caused by neurotrophic changes has been well documented in patients with herpes simplex keratitis, diabetes, and leprosy and in those undergoing ocular surgery (1–5). Mechanical factors also reduce corneal sensitivity in contact lens wearers (6,7). Hyposecretion of tears resulting from a variety of local or systemic disabilities may affect both cornea and conjunctiva. Decreased corneal sensitivity in dry eye may be overlooked, and corneal integrity may be threatened by leaving an open path for possible infection. To recognize such problems, the extent of the reduction in corneal sensitivity should be determined. In this study, we evaluated corneal sensitivities and tear function parameters in patients with dry eye and in an age- and sex-matched control group.

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PARTICIPANTS AND METHODS

Subjects

We studied 59 dry-eye patients. Dry eye was diagnosed according to the criteria applied at our institution (Table 1) (8). Patients were asked to record their symptoms of dry eye on questionnaires before ocular examination. After ocular and serologic examinations, patients were divided into two groups (9), 15 with Sjögren syndrome (SS) dry eye (age, 54.6±9.8 years; 93.3% women) and 44 with non-SS dry eye (age, 52.5±13.3 years; 93.2% women), following the diagnostic criteria of Fox et al. (10).

The control subjects consisted of 26 individuals (age, 50.2±14.0 years) of both sexes (84.6% women) who had no symptoms of dry eye (8), ocular surface abnormalities, systemic diseases related to dry eye, or history of neurologic diseases. They were recruited from among the patients with refractive errors or cataracts in an ophthalmic outpatient clinic. Participants entering this study met the following requirements: they were cooperative with the examiner, they were taking no corneal anesthesia or wearing contact lenses, they had no systemic neurological problems, and they had had no eye surgery.

Measurement

Corneal sensitivity was measured using the esthesiometer of Cochet and Bonnet (11). By changing the length of the nylon filament, the extent of the force applied to the cornea can be varied, and cor-

TABLE 1. *Criteria for diagnosis of dry eye*

Criteria for inclusion
Chronic ocular symptoms
Vital staining test: rose bengal score ≥3 or fluorescein score ≥1
Tear evaluation test: tear film breakup time ≤5 s or Schirmer test with anesthesia ≤5 mm
Criteria for exclusion
Trichiasis
Foreign bodies

neal sensation can be quantitated. A table to convert the length of the filament to the values of the corneal pressure (g/mm^2) is provided with the instrument.

Briefly, the nylon thread of the instrument was extended to a length of 6.0 cm and applied perpendicularly to the center of the cornea. Low pressure was exerted, and the length of the filament was decreased gradually (with 0.5-cm descent) until the first response, such as blinking or startling, occurred. The maximum length of the filament needed to elicit the response was recorded as an indicator of corneal sensitivity.

The Schirmer test with anesthesia and tear clearance rate test were performed 5 min after instilling a 10-μl drop of 0.5% fluorescein and 0.4% oxybuprocaine hydrochloride into the conjunctival sac. The Schirmer strip was then applied for another 5 min. The length of the wet portion was defined as the Schirmer value with anesthesia; the faded fluorescein color was compared with a standard color plate to determine the tear clearance rate. The rate at which the fluorescein color faded on the Schirmer strip was graded as 1, ½, ¼, ⅛, 1/16, 1/32, 1/64, 1/128, or 1/256. The grade of the tear clearance rate defined from 1 (the color of undiluted 0.5% fluorescein solution) to 1/256 (no apparent staining on the Schirmer strip) is based on titer changes of the fluorescein concentration in the conjunctival sac. The tear function index was calculated from the quotient of the Schirmer value with anesthesia and the tear clearance rate (12): tear function index = value of the Schirmer test with anesthesia/tear clearance rate.

For slit-lamp microscopic examination of the ocular surface, we used a micropipette, instilling a 2 μl-drop of preservative-free dye (a combination of 1% rose bengal and 1% fluorescein) into the conjunctival sac (13). Rose bengal staining for the temporal conjunctiva, cornea, and nasal conjunctiva was graded from 0 to 3 (12,14). Fluorescein staining was also graded from 0 to 3 for the upper, middle, and lower thirds of the cornea. After staining of the ocular surface with rose bengal and fluorescein, the esthesiometer procedure was conducted. The Schirmer test with anesthesia and the tear clearance rate were measured 1 h after staining. In addition, the Schirmer test without anesthesia was performed at a follow-up visit.

Data Processing

Data were processed using Stat View software (1988; Abacus Concepts, Inc., CA, U.S.A.) for determination of simple regression and analysis of variance. A level of $p < 0.05$ was accepted as noting statistical significance.

RESULTS

Table 2 lists the test results for patients with dry eye and controls. The mean corneal sensitivity in either dry-eye group was significantly lower than that in the controls ($p < 0.001$; Fig. 1). No significant difference was found between the two dry-eye groups ($p > 0.05$).

Corneal sensitivity correlated significantly with values of the Schirmer test with anesthesia (r =

TABLE 2. *Test results in patients with dry eye and controls (mean ± SD)*

Test	Non-SS dry eye	SS dry eye	Control	p value
Corneal sensitivity (cm)[a]	4.6 ± 1.2	4.5 ± 1.2	5.8 ± 0.4	<0.01[d]
Schirmer test with anesthesia (mm/5 min)	4.5 ± 2.9	3.3 ± 2.0	8.8 ± 6.9	<0.05[e]
Tear clearance rate	1/11.5 (G)[c]	1/11.1 (G)[c]	1/14.6 (G)[c]	—
Tear function index[b]	5.5 ± 1.8	4.9 ± 1.4	6.7 ± 1.1	<0.01[e]
Schirmer test without anesthesia (mm/5 min)	6.4 ± 8.2	4.4 ± 4.8	18.4 ± 9.2	<0.01[d]
Rose bengal score	3.3 ± 2.1	5.6 ± 2.1	0.5 ± 0.7	<0.01[d]
Fluorescein score	2.2 ± 1.6	3.4 ± 1.8	0.2 ± 0.4	<0.01[d]

SS, Sjögren's syndrome.
[a] Determined by the length of the nylon filament.
[b] Logarithm-transformed data, $\log_2$ (tear function index).
[c] Geometric mean.
[d] The p values were significant between both types of dry eye and controls (paired t test, two tails, $p < 0.05$).
[e] The p value was significant between SS dry eye and controls (paired t test, two tails, $p < 0.05$).

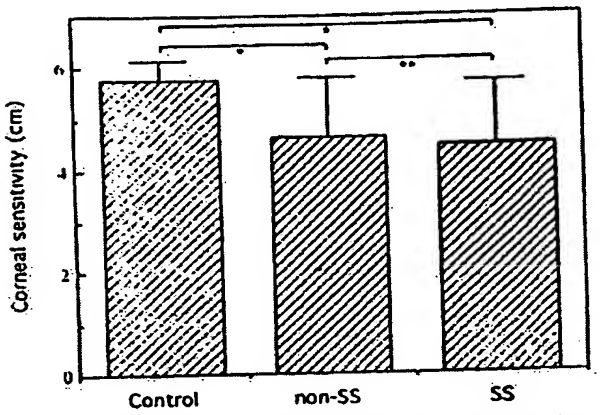

FIG. 1. Mean corneal sensitivity (length of the nylon filament in centimeters) in non-SS dry eye, SS dry eye, and controls (4.6±1.2, 4.5±1.2, and 5.8±0.4, respectively). There were significant differences between both dry-eye groups and the control group (asterisk signifies $p < 0.001$). No significant difference was noticed between the two dry-eye groups (**$p > 0.05$).

0.54, 0.46, and 0.32, for non-SS dry eye, SS dry eye, and controls, respectively; $p < 0.05$). Positive correlations were also found between the corneal sensitivity and the tear function index (Fig. 2). However, no significant relationship was found between the corneal sensitivity and the tear clearance rate or the Schirmer value without anesthesia.

Corneal sensitivity correlated significantly with ocular surface conditions, as determined by rose bengal scores. Figure 3 shows that the better the conditions of the ocular surface, the greater the corneal sensitivity.

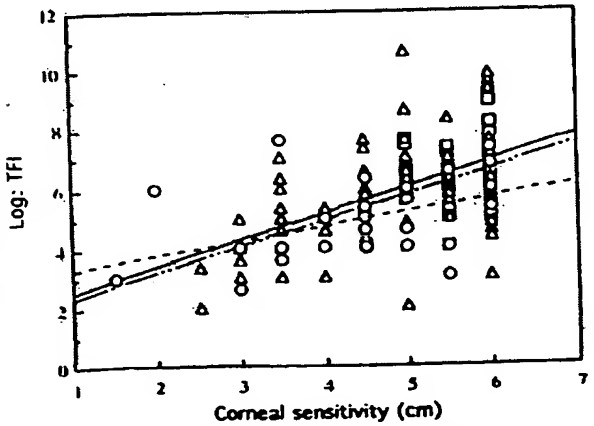

FIG. 2. Corneal sensitivity correlated significantly with the tear function index (TFI) in all three groups (r = 0.53, 0.44, and 0.29 for non-SS dry eye, SS dry eye, and controls, respectively; $p < 0.05$). The higher the tear function index, the greater the corneal sensitivity in all three groups. Symbols (triangle, circle, and square) stand for subjects of non-SS dry eye, SS dry eye, and controls, respectively. Lines (solid/broken, broken, and solid) represent regression for non-SS dry eye, SS dry eye, and controls, respectively.

DISCUSSION

In the present study we show that individuals with dry eye have a greater incidence of reduced tactile sensitivity of the cornea than do controls. The reduced corneal sensitivity appears to be re-

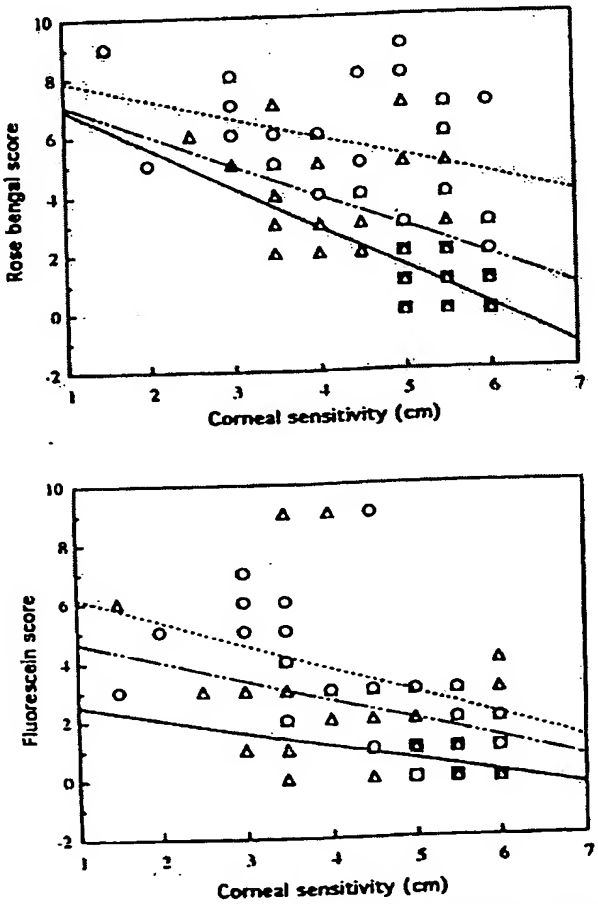

FIG. 3. Significant relationships were observed between corneal sensitivity and rose bengal scores (r = 0.58, 0.38, and 0.68 for non-SS dry eye, SS dry eye, and controls, respectively; $p < 0.05$) and fluorescein scores (r = 0.48, 0.55, and 0.40 for non-SS dry eye, SS dry eye, and controls, respectively; $p < 0.05$). Symbols (triangle, circle, and square) stand for subjects of non-SS dry-eye, SS dry-eye, and control groups, respectively. Lines (solid/broken, broken, and solid) represent regression in non-SS dry eye, SS dry eye, and controls, respectively.

lated to disturbance of the ocular surface integrity, which results from impaired tear secretion. Corneal nerves, apart from the sympathetic supply to the vascular plexus at the limbus, are derived from the ophthalmic division of the fifth cranial (trigeminal) nerve. The afferent pathway leaving the corneal sense organ extends into the ophthalmic nerve and then joins the major trigeminal trunk. Corneal nerve fibers have two types of endings: numerous fine, threadlike filaments between the lamellae and penetrating apertures through Bowman's membrane reaching the four basal layers of the corneal epithelium (15). The maintenance of corneal physical properties is highly dependent on an adequate nutritional supply from perilimbal capillaries, the tear fluid, or the aqueous humor. A substantial portion of the oxygen required by the cornea is supplied through the external surface; presumably, the tear fluid dissolves oxygen and diffuses into the epithelium.

The development of dry eye is based on changes in composition of the tear film, the outmost oil layer from the meibomian glands, the water layer from the lacrimal gland, or the innermost mucinous layer from the goblet cells of the conjunctiva. The mucous tear layer is thought to play a major role in maintaining the protective status of the precorneal tear film (16). Moreover, tear film stability is controlled by the ocular surface epithelium (16). Based on clinical staining and impression cytology (17), the features characteristic of keratoconjunctivitis sicca are positive rose bengal staining and squamous metaplasia (16,17). These changes may represent the alteration of the precorneal tear film and epithelial cells of the cornea and conjunctiva in dry eye. Increased staining has been observed to correlate with decreased corneal sensitivity in our study, partly reflecting disease severity.

Dry-eye patients have symptoms of irritation because of the impairment of the ocular surface. However, perception of pain was paradoxically lessened in these patients. From the physiologic standpoint, sensory nerves may adapt to a stimulation; the frequency and intensity of action potentials may decline in adaptation. The process involves simple accommodation of the axon (18). The pain receptors of the cornea belong to a class of slowly adapting end organs. Prolonged erosion and irritation of the ocular surface may elevate the threshold for pain; thus stronger stimuli are required to elicit corneal sensation in patients with dry eye.

Imbalance in tear dynamics (i.e., tear production, tear evaporation, or tear drainage) is the leading cause of dry eye. Derived from the Schirmer test with anesthesia, the tear function index is a good indicator of tear secretion and drainage (12); the higher the tear function index, the better the ocular surface condition. That corneal sensitivity correlated significantly with the Schirmer values with anesthesia and the tear function index suggests that the decline in basic tear secretion in dry eye may exert an influence on corneal hypoesthesia. Moreover, characteristic staining on the ocular surface correlated with decreased corneal sensitivity in dry eye, indicating that tear deficiency may have an impact on ocular surface impairment and act as a facilitator of corneal hypoesthesia.

While exploring the relationship between corneal sensitivity and tear dynamics, we analyzed data dealing with tear drainage and reflex tearing. In a previous study, we compared results of the tear clearance rate with those of the basal tear turnover and tear flow obtained from fluorophotometry. We found that each higher grade of the tear clearance rate showed a 12.5% increase in basal tear turnover (3.59%/min) and tear flow (0.38 μl/min) (19).

We believe that the tear clearance rate and the Schirmer test without anesthesia measure tear drainage and reflex tear secretion, respectively. However, results of these tests did not correlate with corneal sensitivity. The validity of these tests has been debated (12,14). The absence of correlation may be attributable to the fact that these tests are less reliable or that the decline in corneal sensitivity is independent of tear drainage and reflex tears.

Considering the variation in cornea sensitivity, we measured all data in the center circular area of ~5 mm in diameter, an area of extreme corneal acuity (20). Although corneal sensitivity was assessed before performing the Schirmer test with anesthesia, it was measured after the instillation of rose bengal and fluorescein. Since many ophthalmic solutions can elevate the threshold of corneal sensitivity (1), inaccuracies are likely. In addition, erosion and irritation of the ocular surface may interfere with patients' affirmative responses to the esthesiometer.

Collectively, decreased tear secretion in dry eye may have an impact on the pathologic changes of the corneal epithelium and lead to a decline in corneal sensitivity. Prompt treatment of dry eye is essential to maintain the normal protective mechanism and prevent the potentially severe complications of this disorder.

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Improvement of Corneal Sensation and Tear Dynamics in Diabetic Patients by Oral Aldose Reductase Inhibitor, ONO-2235: A Preliminary Study

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The mechanism in the pathogenesis of diabetic corneal disease is unclear, but aldose reductase may be involved in the corneal disease. We studied the effects of an aldose reductase inhibitor (ARI) on the ocular surface of diabetic patients. Fourteen aphakic or pseudophakic patients with diabetes were treated with orally administered ONO-2235 (150 mg/day). Corneal sensation, vital staining of ocular surface, and tear production were examined before and 3 months after the administration. After a 3-month period of oral ARI, corneal sensation recovered significantly (from 4.1±4.8 to 3.0±3.1 g/mm^2; $p = 0.015$), with parallel improvements in rose bengal and fluorescein staining scores ($p < 0.05$). Tear break-up time had also improved ($p = 0.003$). Results of Schirmer's test ($p = 0.03$) and the cotton-thread test ($p = 0.0001$) showed significant improvement in tear production. Improvement in the dynamics of tear production may be due to an improvement in corneal sensitivity. An oral ARI can improve corneal epithelial changes caused by diabetes, probably through recovery of corneal sensation and tear production.
Key Words: Aldose reductase inhibitor—Corneal sensation—Tear dynamics—Tear break-up time.

Cataract, retinopathy, and iritis are well-known complications of diabetes mellitus. The corneal epithelium of diabetics also suffers severely, especially after vitreous surgeries, and recently problems involving the ocular surface have been reported in patients with diabetes mellitus, particularly after ocular surgery (1–3). Patients with diabetes experience a variety of corneal complications, irrespective of ocular surgery (4–8), including superficial punctate keratopathy (5), recurrent corneal erosion (9), persistent epithelial defect, or trophic ulceration (10). The mechanism responsible for diabetic ocular surface abnormality is unclear, but aldose reductase, the first enzyme of the sorbitol pathway, may be involved, as it affects other tissues in diabetic complications (11–13). A neurotrophic involvement is suggested by the observation that diabetics show a decrease in corneal sensitivity (6) and by the complications of sterile ulcers in corneas of diabetics (10). Experimental studies showed that aldose reductase inhibitors (ARIs) are effective in promoting corneal reepithelialization (14–16), and the topical ARI, CT-112, was reported to improve corneal sensitivity (17); clinical benefit was also reported (18). Morphologic study with specular microscopy was performed and showed capability in reversing abnormal morphologic characteristics of corneal epithelial cells in diabetic patients (17). However, no information has been reported about the effects on tear dynamics. In our study, we administered an ARI, ONO-2235 {(E)-3-carboxymethyl-5-[(E)-2-methyl-3-phenylpropenylidene] rhodanine}, orally for 3 months to 14 diabetic patients after cataract surgery and examined whether it could improve the ocular surface condition. We also showed that three typical cases of post-cataract surgery patients with diabetic corneal abnormality seemed to show a dramatic response to treatment with the ONO-2235.

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MATERIALS AND METHODS

Patients

Diabetic patients who had undergone bilateral cataract extraction and implantation of posterior-chamber intraocular lenses were enrolled in this study. All patients had had surgery ≥3 months before the study (range, 3–24; average, 12.1±5.8) (Table 1). Their clinical abnormalities included two cases of corneal ulcers, two cases of epithelial defect, and 10 cases of superficial punctate keratopathy; all had symptoms such as foreign-body sensation (18,19). The study group comprised 14 pseudophakic patients with diabetes (seven men and seven women; mean age, 62.9±7.5 years). Five patients had nonproliferative retinopathy, seven had preproliferative retinopathy, and two had proliferative retinopathy. The types of diabetes were non-insulin-dependent diabetes mellitus (NIDDM) in nine patients and insulin-dependent diabetes mellitus (IDDM) in five others. The mean duration of diabetes was 13.8±1.0 years, and the mean duration of diabetic retinopathy was 3.7±1.0 years. In four patients, photocoagulation had been performed, and one patient had undergone vitrectomy.

Drug Administration

After explaining the nature of the study to the patients, we administered ONO-2235, total 150 mg/day, three times daily, 30 min before each meal, for 3 months. No other drug with known or suspected interactions with ONO-2235 or any systemic and topical drugs that have effects on tear production or ocular surface was prescribed during the study.

TABLE 1. *Profile of patients*

Patient no.	Age	Sex	Retinopathy	Time from surgery (mo)
1	63	M	Pre-	7
2	53	F	Non-	16
3	57	M	Pre-	3
4	58	M	Pre-	18
5	79	M	Pre-	11
6	68	M	Proliferative	6
7	67	F	Non-	17
8	70	F	Pre-	6
9	67	F	Non-	14
10	58	M	Non-	12
11	63	F	Pre-	11
12	64	M	Pre-	24
13	53	F	Proliferative	8
14	71	F	Non-	16
Average	62.9			12.1

Pre-, preproliferative; Non-, nonproliferative.

Clinical Examination

Corneal sensation, rose bengal and fluorescein stains, tear break-up time (BUT) (20), Schirmer's test, and the cotton-thread test (21) were all used for evaluation of the ocular surface. Central corneal sensation was measured with a Cochet and Bonnet aesthesiometer (Luneau Ophthalmologie, Prunay-le-Gillon, France) (22). Rose bengal staining was graded 0 to 3+ at the nasal conjunctiva, the temporal conjunctiva, and the cornea, with a maximal grade of 9+ (23). Fluorescein staining was graded 0 to 9+ at the cornea (23). BUT was the number of seconds between the last complete blink and the first disturbance of the precorneal tear film. Schirmer's test was performed 5 min after instillation of a drop of solution containing 0.5% fluorescein and 0.4% oxybuprocaine hydrochloride into the cul-de-sac (18).

Each measurement was made by the same investigator (H.F.) in the same room. All patients gave their informed consent for participation in this study.

Statistical Analysis

Data were reported as real numbers. Statistical analysis used the paired t test. Probability values <0.05 were considered statistically significant.

RESULTS

Before treatment, corneal sensation in these patients was 4.1±4.8 g/mm^2 (mean ± SD). After a 3-month period of oral ONO-2235 administration, corneal sensation was significantly improved to 3.0 ± 3.1 g/mm^2 ($p = 0.015$). Recovery of corneal sensation paralleled improvements in the rose bengal staining score (from 1.9±1.7 to 1.0±1.3; $p = 0.03$), and the fluorescein staining score (from 2.9±1.9 to 1.6±1.7; $p = 0.02$). Tear BUT improved from 2.5±1.1 s to 3.4±1.0 s ($p = 0.003$). Measurement of tear production, such as Schirmer's test, improved from 7.5±3.8 mm before treatment to 8.8±4.5 mm after treatment ($p = 0.03$). The score on the cotton-thread test increased from 22.1±6.8 mm before treatment to 27.4±7.8 mm after treatment with ONO-2235, a significant improvement ($p = 0.0001$) (Table 2). No side effects were seen in this treatment.

Representative cases with three types of corneal abnormality were shown:

Case 1, a 57-year-old man with diabetes, developed a corneal ulcer in the right eye 3 months after the cataract surgery, and it remained for a month in spite of conventional topical therapy (Fig. 1A).

TABLE 2. *Changes in ocular surface condition and tear production after treatment with oral ARI*

	Corneal sensation (g/mm^2)	BUT (s)	RB	Fluoresceln	Schirmer (mm)	Cotton (mm)
Pretreatment	4.1 ± 4.8	2.5 ± 1.1	1.9 ± 1.7	2.9 ± 1.9	7.5 ± 3.8	22.1 ± 6.8
After-treatment	3.0 ± 3.1	3.4 ± 1.0	1.0 ± 1.3	1.6 ± 1.7	8.8 ± 4.5	27.4 ± 7.8
p Value (*t* test)	0.015	0.003	0.03	0.02	0.03	0.0001

ARI, aldose reductase inhibitor; BUT, break-up time; RB, rose bengal.

Then 150 mg/day of ONO-2235 was administered, and the ulcer healed within 1 month (Fig. 1B).

Case 2, a 68-year-old man with diabetes, developed a corneal epithelial defect in the right eye 6 months after the cataract surgery, and it remained for 4 months in spite of conventional topical therapy (Fig. 2A). Then 150 mg/day of ONO-2235 was administered, and the ulcer defect healed within 2 months (Fig. 2B).

Case 3, a 64-year-old man with diabetes, developed recurrent superficial punctate keratopathy in both eyes 2 years after the cataract surgery, and it remained in spite of topical treatment (Fig. 3A). Then 150 mg/day of ONO-2235 was administered, and the keratopathy disappeared within 3 months (Fig. 3B).

DISCUSSION

Surgical improvements have made many diabetic patients candidates for cataract surgery, and diabetic corneal abnormality has become of major clinical significance after such operations. Diabetes causes a variety of clinical complications (24). Various conditions are responsible for retinal hypoxia, but recently the possibility that it is due to metabolic abnormalities associated with hyperglycemia, such as an activation in polyol pathway, has received worldwide attention. The rate-limiting enzyme in this metabolic pathway is aldose reductase. Theoretically, inhibition of this rate-limiting enzyme in the pathway of polyol metabolism results in a reduction of impaired functions of and histologic changes in nerves. Thus it has been reported that the onset and progression of diabetic complications can be prevented by ARIs (11,25–27).

In this study, corneal sensation was significantly improved. Evidence of diabetic keratopathy is detectable relatively early after the onset of diabetes, manifesting itself as decreasing corneal sensation and a variety of clinical symptoms (11,26,28). As Hosotani et al. (17) reported that topical CT-112 reduced corneal sensitivity in diabetic patients, ARIs might have improved the sensitivity by oral administration.

Jordan and Baum (29) demonstrated, by using fluorophotometry, that topical proparacaine decreases tear secretion in the human eye by 60 to 75%. Improvement in the dynamics of tear production may be the result of an improvement in corneal sensitivity, probably caused by effective suppression of aldose reductase activity in the Schwann cells (30).

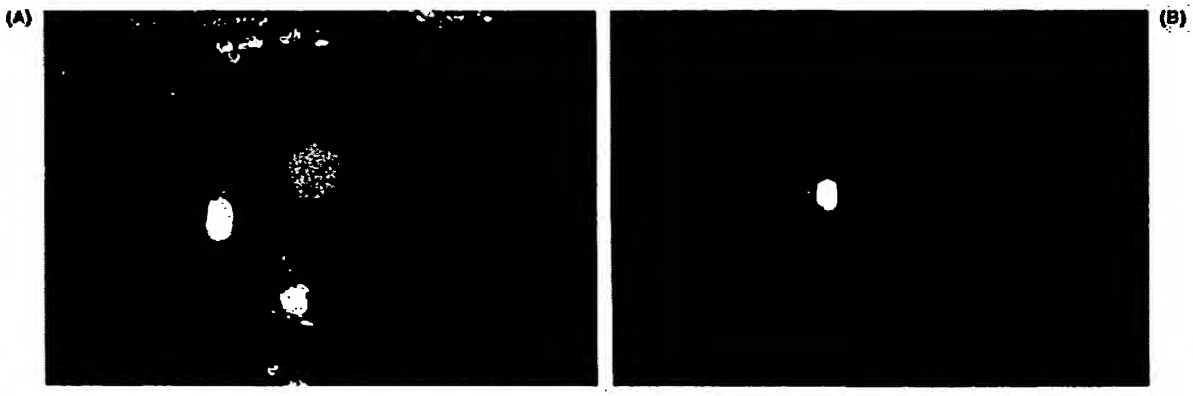

FIG. 1. A typical case of improvement of corneal ulcer (patient 3). **A:** Corneal ulcer was seen in the right eye and remained for a month before the treatment of ONO-2235. **B:** Cornea was almost clear 1 month after the administration of ONO-2235.

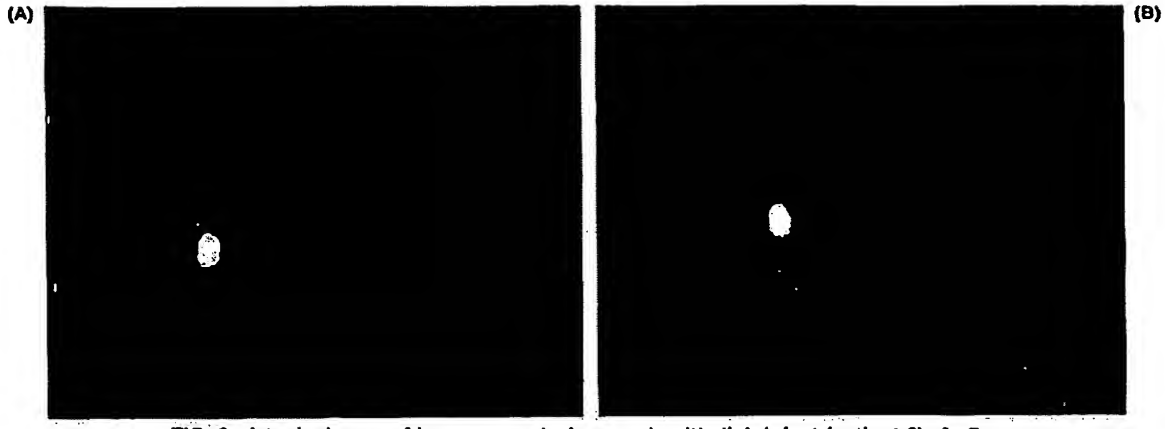

FIG. 2. A typical case of improvement of corneal epithelial defect (patient 6). A: Corneal epithelial defect was seen in the right eye and remained for 4 months before the treatment of ONO-2235. B: Cornea was almost clear 2 months after the administration of ONO-2235.

Improvement of tear dynamics, of which figures are below normal but indicate significant improvement, might improve such conjunctival and corneal abnormalities as "dry eye." Improvements in rose bengal and fluorescein staining scores and reduction of the debris in tears may be attributable to improved tear dynamics.

Gilbard et al. (31) showed that topical proparacaine increases tear-film osmolarity in rabbit eyes, and they postulated that the increase results from decreases in tear secretion secondary to decreased ocular surface sensitivity. The increase in tear BUT may also be due to the improvement of tear-production dynamics or corneal sensitivity. All these significant improvements, especially dramatic improvement of corneal ulcers or ocular-surface conditions, may be due to this drug.

Although surgery causes a more serious clinical problem (1,9) because of impairment of the corneal nerve (a manifestation of diabetic neuropathy) (4,5, 10,32), and it has been reported that extracapsular cataract extraction decreases the corneal sensitivity in triangular shape (33), we cannot deny the possibilities of the spontaneous improvement of corneal sensation and ocular-surface condition in these cases. However, this improvement was thought to

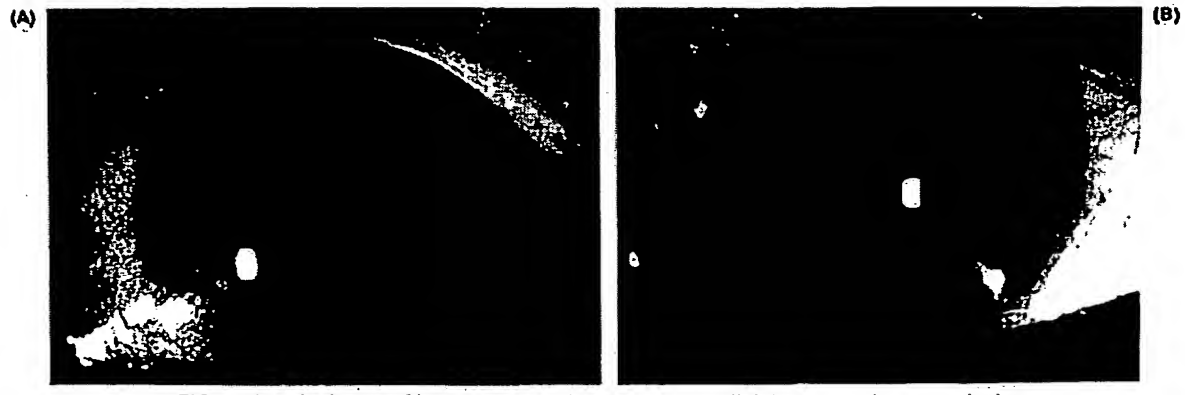

FIG. 3. A typical case of improvement of recurrent superficial punctate keratopathy in right eye (patient 12). A: Superficial punctate keratopathy was seen in both eyes and remained for 2 years before the treatment of ONO-2235. B: Cornea was almost clear 3 months after the administration of ONO-2235.

be due to oral ONO-2235 because the duration from the cataract surgery was 12.1 months.

In our preliminary study, after treatment with oral ONO-2235, 150 mg/day for 3 months, there was significant recovery of diabetic abnormalities including ocular-surface disorders and tear production. This study was an open-label trial in that both the patients and examiner were aware that active medication was being given. This would provide bias for many results and influence this study. To explore the questions of real effect of the ARI on clinical safety and benefits, we are conducting a randomized and controlled clinical study of ONO-2235. In an animal study of serum density, Miyamoto et al. (34) reported that the serum density of oral ONO-2235 amounted to a maximum density at 15 min after oral administration in a male rat. The choroidal density peaked from 1 to 3 h after oral single administration, and the density was almost 20% of serum density in a male rat. This drug, 150 mg/day of ONO-2235, is safe and may most likely be an effective treatment for human eyes.

In conclusion, the administration of ONO-2235, an ARI, to patients with diabetic ocular-surface conditions for 3 months led to improvements in tear dynamics and in the signs and symptoms of post-cataract extraction keratopathy of the patients with diabetes.

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